distributing forces across subsystems, and to preserve the integrity of FG molecules when the system is simulated close to the CG limit.
The benchmark was applied to liquid hexadecane. The temperature-scaling scheme achieved a threefold sampling speedup with little deviation of FG properties. The multigraining scheme kept FG properties the best but provided little sampling speedup. The mass-scaling scheme also yielded a threefold speedup but deviated the most from FG properties.

3240-Plat
Caveolin in Bilayers: Can the Intramembrane U-Shaped Conformation Really Exist
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Caveolin induces membrane curvature and drives the formation of caveolae that participate in many crucial cell functions such as endocytosis. The central portion of caveolin-1 contains two helices (H1 and H2) connected by a three-residue break with both N- and C-termini exposed to the cytoplasm. Although a U-shaped configuration is assumed based on its inaccessibility by extracellular matrix probes, caveolin structure in a bilayer remains elusive. This work aims to characterize the structure and dynamics of caveolin-1 (D82 to S136; $Cav1_{82\text{-}136}$) in a DMPC bilayer using NMR, fluorescence emission measurements, and molecular dynamics (MD) simulations. The secondary structure of $Cav1_{82\text{-}136}$ from NMR chemical shift indexing analysis serves as guideline for generating initial structural models. 50 independent MD simulations (80 ns each) are performed to identify its favorable conformation and orientation in the bilayer. Using the short simulations as a guideline, a representative configuration was chosen and simulated for 1 μs to further explore its stability and dynamics. The results of these simulations mirror those from the tryptophan fluorescence measurements (i.e., $Cav1_{82\text{-}136}$ insertion depth in the bilayer), and corroborate that $Cav1_{82\text{-}136}$ inserts in the membrane with a U-shaped conformation. The angle between H1 and H2 ranges from 35° to 69°, and the tilt angle of $Cav1_{82\text{-}136}$ is 27° ± 6°. The simulations also show that specific faces of H1 and H2 prefer to interact with each other and with lipid molecules, and these interactions stabilize the U-shaped conformation.

Platform: Ligand-gated Channels II

3241-Plat
Coordinated Movements During ASIC1A Activity
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Acid-sensing ion channels (ASICs) are H^+-gated and Na^+-conducting channels predominantly expressed in the nervous system. They are involved in H^+ sensing in many physiological and pathological states such as ischemia and pain perception. The crystal structure of the chicken ASIC1 isoform has been revealed in the desensitized and the open state. Functional studies indicate that protonation of key residues in the extracellular loop triggers conformational changes leading to channel opening. However the molecular mechanisms linking protonation to the opening and closing of the gate have not been clarified yet. In this study we used voltage-clamp fluorometry (VCF) to reveal activity-associated movements occurring on the different ASIC1a domains. 20 different fluorophore positions located in the thumb, palm, finger and knuckle domains and in the extracellular pore entry showed VCF signals related to conformational changes. The timing of fluorescence changes suggests a complex sequence of movements upon pH change. When the pH of the extracellular solution was lowered to activate ASICs, rapid conformational changes were observed in the thumb, finger, knuckle and extracellular pore entry, followed by slower movements in the palm. The kinetics of fluorescence and current signals were compared to each other in order to assess whether the timing of the fluorescence signal corresponded to an effective channel transition. Some of the residues tested were found to be closely related to channel opening, desensitization or recovery from desensitization. Moreover we found that an endogenous tryptophan of the β-ball quenched the fluorescence signal of probes positioned in the finger and knuckle domains. The observed increase of this signal during channel opening indicates a movement of these domains away from the β-ball. This is the first extensive analysis of activity-dependent conformational changes in ASICs which could be applied to other ENaC-Deg related channels.

3242-Plat
Optochemical Control of Engineered Trimeric P2X Receptors and Acid-Sensing Ion Channels
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P2X receptors are trimeric membrane ion channels activated by extracellular ATP. Elucidation of their physiological roles has been handicapped by a lack of specific tools. In the present work, the P2X2 receptor was engineered to open and close with different wavelengths of light. We synthesized a photoswitchable crosslinker, bis(maleimido)azobenzene, of molecular dimensions appropriate to bridge cysteines introduced at different subunits at the outer pore (P329C). This produced a P2X2 receptor that was opened within milliseconds at 440 nm light and closed rapidly at 360 nm light, as measured by the ionic currents. When the P329C mutation was combined with the ATP-binding site mutation, K69A, ATP had no effect while light-induced currents were still present. The light-gated receptor displayed similar unitary currents, inward rectification and calcium permeability (PCa/PNa = 2.6), as the P2X2 receptors activated by ATP. P2X3 receptors with an equivalent mutation (P320C) could be controlled with light, displaying typical rapid desensitization. P2X3 [P320C] subunits also co-assembled with native P2X2 subunits in pheochromocytoma 12 cells to form light-gated heteromeric P2X2/3 receptors. We extended this approach to acid-sensing ion channels (ASICs), which are also trimers but are unrelated in sequence to P2X receptors. The structurally equivalent mutation in human ASIC1 (G430C) was readily opened and closed by brief applications of light following modification with bis(maleimido)azobenzene. This provides functional evidence that P2X receptors and ASICs can open by a similar mechanism at the level of the pore. The generation of these engineered receptors should facilitate investigation of the functional roles of P2X receptors and ASICs in the cell, tissue and intact organism.

3243-Plat
X-Ray Structures of the Open and Resting Forms of the Same Bacterial Pentameric Ligand-Gated Ion Channel
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Pentameric ligand-gated ion channels (pLGIC) mediate fast chemical transmission of nerve signals. The structure of GLIC, a bacterial proton-gated homolog, has been established in its open and Locally Closed (LC) conformations at acidic pH. Here we report its crystal structure at neutral pH, revealing for the first time the two end-points of the gating mechanism in the same pLGIC using X-ray structures. The structural variability in the neutral pH structure observed in the crystal due to the presence of four copies in the asymmetric unit can be used to analyse the intrinsic fluctuations in this state. It is found that they have a marked tendency to occur in the direction of the closed-to-open transition. In the extra-cellular domain (ECD), an important quaternary change is observed, involving both a twist and a blooming motion, while the transmembrane channel (TMD) is closed in an LC-manner. On the tertiary level, detachment of inner and outer beta-sheets in the ECD reshapes two essential cavities at the ECD-ECD and ECD-TMD interfaces. The first one is the ligand-binding cavity, the other is a new one that matches a known Ca^{++} or Zn^{++} binding site in some pLGICs. These results shed new light on the allosteric transitions of pLGIC and their pharmacology. In addition, a plausible pathway between the two forms is presented and discussed.

3244-Plat
Structural Basis for Allosteric Coupling at the Membrane-Protein Interface in GLIC
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Ligand-binding at the extracellular domain of pentameric ligand-gated channels, initiates a relay of conformational changes that culminates at the gate within the transmembrane domain. The interface between the two domains is a key structural entity that governs gating. Molecular events in signal transduction at the interface are poorly defined due to its intrinsically dynamic nature